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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,323	12/23/2004	Hans Loibner	4518-0107PUS1	9319

2292 7590 09/24/2007

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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
09/24/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/519,323	LOIBNER ET AL.	
	Examiner	Art Unit	
	Meera Natarajan	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1,17,18 and 22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2-16,19-21,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claim 2 and species election for humanized antibody, Lewis-y structure, and administration in combination with a carrier in the reply filed on 07/25/2007 is acknowledged. The traversal is on the ground(s) that the reference the Examiner cited in the requirement for restriction (Blaszczyk-Thurin et al.) does teach a murine monoclonal antibody BR55-2 which is directed to the LEWIS Y antigen however it does not support that the antibody can be used to treat tumor cells in a cancer patient. The applicant is correct in pointing out that Blaszczyk-Thurin et al. does not teach this limitation, however as stated in the restriction requirement "groups I-IV share a common technical feature, an antibody directed against a tumor associated glycosylation. The antibody of Claim 1 cannot be a **special** technical feature under PCT Rule 13.2 because it is shown in the prior art. Therefore, this argument is not found persuasive and the requirement is still deemed proper and is therefore made FINAL.

2. Applicant has amended claims 3-16 and 19-21 to depend upon the method of treatment in Claim 2, and Claims 27 and 28 have been added as also directed to the method of treatment of Claim 2. Therefore Group II is now directed to Claims 2-16, 19-21, 27 and 28.

3. Claims 1, 17, 18, 22-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/25/2007.

4. Claims 2-16, 19-21, 27 and 28 will be examined on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 4-7, 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 2 recites "an antibody directed against a tumor-associated glycosylation". It is unclear whether the antibody is directed to a "glycosylated tumor cell receptor" (recited in line 2 of Claim 2) or an antibody directed to any glycosylated tumor-associated protein?

8. Claim 4 recites, "treating a chemotherapy-resistance". It is unclear what "chemotherapy-resistance" is referring to. Is the patient chemotherapy resistant? Are the cancer cells of the patient resistant to chemotherapy? Clarification is required.

9. Claim 5 recites the limitation "the minimal residual disease" in line 2. There is insufficient antecedent basis for this limitation in the claim. It is unclear if the treatment results in "minimal residual disease". Clarification is required.

10. Claim 6 recites the limitation "the mitogenic stimulation" in line 2. There is insufficient antecedent basis for this limitation in the claim.

11. Claim 7 recites the limitation "the lysis of tumor cells" in line 1. There is insufficient antecedent basis for this limitation in the claim.

12. The term "most preferred" in claim 13 and "preferably" in claim 14 are relative terms which render the claims indefinite. The terms "most preferred" and "preferably" are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 2, 4, 5, 7-11 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Saleh et al. (J. of Clinical Oncology, Vol. 18, No. 11:2282-2292 June 2000) as evidence by Basu et al. (Cancer Research Vol. 47:2531-2536, May 1987), Kumar et al. (Seminars in Oncology Vol. 28 pp.27-32, 2001) and the instant specification.

15. The claims are drawn to a method of treatment comprising administering to a cancer patient an antibody directed against the aberrant glycosylation of a tumor-associated antigen, Lewis Y, to inhibit or reduce the growth of tumors cells in said patient by inhibiting EGF binding to its receptor.

16. Saleh et al. teach the administration of an antibody (BR96) directed against the tumor associated glycosylated antigen, Lewis-Y. The immunoconjugate BR96-Doxorubicin, which is the chimeric immunoglobulin (Ig)G1 anti-Lewis Y monoclonal antibody BR96 linked to the anthracycline doxorubicin (see p. 2282, right column, lines 9-12), to patients with metastatic colon or breast cancer who have failed no more than two prior chemotherapeutic regimens and their disease has not progressed while on doxorubicin-based therapy (defined as chemotherapeutic resistant (claim 4) and "minimal residual disease" (claim 5) in the specifications of the instant application p. 2 paragraph 6 and p. 4 paragraph 4). The colon and breast cancer patients in the study taught by Saleh et al. would inherently express a receptor from the family of the EGF receptors (Claim 16) because it is well known in the art that colon and breast cancer tissues express aberrant levels of EGF receptors (see Abstract, Kumar et al. Seminars in Oncology 2001). Basu et al. supports the inherency claim that all Lewis Y antibodies would bind to the EGF receptor because these antigens are intrinsic to the EGF receptors of all antigen-positive carcinoma cells. Basu et al. discloses "cell lines which react with anti-Lewis Y antibodies express these antigens on their surface glycolipids and glycoproteins, including the EGF receptor (see Abstract and p.2532 right column last paragraph through p. 2533 left column). It would also be inherent that the cells of the cancer patient exhibit aberrant glycosylation (claim 9) as it is stated in the instant specification that "treatment of patients with tumor cells with aberrant glycosylation becomes possible, e.g. tumor cells having a receptor from the EGF receptor family, or Lewis y-positive tumor cells" (see p. 8, lines 13-16). Saleh et al. also disclose doses

(claim 14) of the antibody at levels of 66-875 mg/m^2 (see Table 3, p. 2285). Therefore, the references teaches all the limitations of the claims.'

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claims 2-16, 19-21, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saleh et al. in view of Queen et al. (Patent #6180370) and Trail et al. (Clinical Cancer Research Vol. 5:3632-3638 November 1999).

20. The claims are drawn to a method of treatment comprising administering to a cancer patient a humanized antibody directed against the aberrant glycosylation of a tumor-associated antigen, Lewis Y, in combination with chemotherapy to inhibit or reduce the growth of tumors cells in said patient by inhibiting EGF binding to its receptor

and an "ex vivo" according to the method of claim 2, characterized in that a body fluid or a tissue from a cancer patient is treated ex vivo.

21. The teachings of Saleh et al. are presented in the 102(b) rejection set forth above. Saleh et al. does not teach the use of a *humanized* anti-Lewis y antibody in combination with chemotherapy and an "ex vivo" method. This deficiency is made up for in the teachings of Queen et al. and Trail et al.

22. Queen et al. (Patent # 6180370) teaches a method for preparing humanized immunoglobulins for novel therapeutic agents. Queen et al. discloses pharmaceutical compositions comprising the humanized antibodies and effector molecules such as chemical agents, proteins, or drugs linked to the antibody for diagnostic use (see columns 19 4th paragraph - column 20 2nd paragraph). Queen et al. also disclose preparing humanized immunoglobulins that retain high binding affinities of at least about $10^{-8} – 10^{-10}$ mol/1 (see column 3 lines 38-40 and column 22, lines 37-42).

23. Trail et al. teach the enhanced anti-tumor activity of Paclitaxel in combination with the anti-carcinoma immunoconjugate BR96-Doxorubicin. Trail et al. demonstrate combined therapy using an anti-carcinoma immunoconjugate, BR96-Doxorubicin, and the cytotoxic drug paclitaxel results in significant increase in anti-tumor activity over that of either agent alone (see Abstract). Combined therapy resulted in increased anti-tumor activity against lung, colon, and breast tumors xenografted in athymic mice. Human lung carcinoma cell lines derived from human tissues that express the BR96-defined antigen (Lewis Y) were also treated with BR96-doxorubicin to evaluate changes in the cell cycle. Exposure of BR96-dox resulted in a significant increase in the percentage of

cells accumulating in G_2-M phase (see Figure 4. p.3637) which means they were not undergoing mitosis (claim 6) because EGF was blocked from binding to the EGF receptor by the anti-Lewis Y antibody (BR96-dox). In addition previous studies have shown that cells are most sensitive to paclitaxel-induced apoptosis (lysis of tumor cells) during the G_o-G_1 and G_2-M transitions of the cell cycle (p. 3635 right column, 1st paragraph). Therefore, with a high percentage of cells arresting in the G_2-M phase, administration of paclitaxel in combination with BR96-dox will result in a higher rate of inducing apoptosis in these tumor cells (claim 7).

24. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a high affinity binding humanized version of the BR96-Dox antibody taught by Saleh et al. to be administered in combination with a chemotherapeutic agent in view of Queen et al. and Trail et al. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success by the teachings of Queen et al. and Trail et al. to have produced a humanized BR96-Dox antibody and used it in combination with paclitaxel to perform an ex-vivo method of treating human tissue samples or cells and a method of treating cancer patients because the target antigen has been shown to be expressed in human cancers (see specifications p.8 lines 13-16).

Conclusion

25. Claims 2-16, 19-21, 27 and 28 are rejected

26. No claim is allowed.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meera Natarajan whose telephone number is 571-270-3058. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN

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SUPERVISORY PATENT EXAMINER